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FULL-LENGTH PAPER

Novel ionic liquid supported-multicomponent reaction toward chimeric *bis*-heterocycles

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Abstract A novel multicomponent reaction between IL-anchored 2-aminobenzoimidazoles, aldehydes, and electron-deficient dienophiles has been explored. The strategy was utilized to develop a rapid parallel synthesis for novel *bis*-heterocyclic skeleton of benzimidazole-linked dihydropyrimidine on an ionic liquid support. This multicomponent reaction is compatible with a wide range of substrates and furnishes the new chimeric scaffolds with high purity and excellent yields. Use of the ionic liquid as a soluble support facilitates purification by simple precipitation along with advantages like high loading capacity, homogeneous reaction conditions, and monitoring of the reaction progress by conventional NMR spectroscopy.

Keywords Multicomponent reaction · MCR · Ionic liquid support · Chimeric scaffolds · [1,5]Sigmatropic rearrangement · Benzimidazole-linked dihydropyrimidine

Introduction

Dihydropyrimidine and benzimidazole derivatives are key structural elements in many biologically active natural products and pharmaceutical compounds. Some of those constitute key intermediates which have widespread applications in drug discovery [1]. For instance, (*R*)-fluorastrol is a potent human kinesin Eg5 inhibitor by disrupting the establishment of the bipolar spindle [2]. MRS 2957 is a selective $P2Y_6$ receptor agonists for the treatment of muscle wasting and neurodegeneration [3]. Raltegravir is a potent, selective orally bioavailable HIV-integrase inhibitor [4]. The benzimidazole derivatives, ZSTK474 and compound A, display highly potent inhibitory activity again pan class I phosphatidylinositol 3-kinase (PI3K) [5] and prolylcarboxypeptidase (PrCP) [6], respectively (Fig. 1). As a consequence of their relevant pharmacological profile, the search for new methodologies to access bi-heterocyclic chimera is an interesting field of current research attention.

Furthermore, the integration of two privileged heterocyclic scaffolds into a novel core skeleton often creates unexpected improvements on the interaction with biological targets and becomes pivotal importance to discover new type of potent modulators [7,8]. Among those known methods are multicomponent reactions (MCRs) [9,10] which offer the opportunity to build up complex molecules in a fast, clean, and efficient way. This class of reaction enables the construction of molecules with great structural complexity with a minimum of manual operations, thereby saving time, effort, and synthetic cost. Moreover, given the current trend on the development of environmental friendly procedures, these one-pot reactions with their easy purification steps are useful alternatives to the classical stepwise approaches. Among many reported methods for the construction of polyheterocyclic chimera, the multicomponent reaction between aniline, aldehyde, and electron-rich olefin stood out as one of the most attractive route [11]. In spite of its versatility, many aspects of this multicomponent reaction have some limitations. For example, the range of aryl amines and dienophiles employed is relatively small since aniline and electron-rich dienophiles can only be used according to the literature. In addition, only protic or Lewis acids were applied as catalysts in all these processes [12,13]. In

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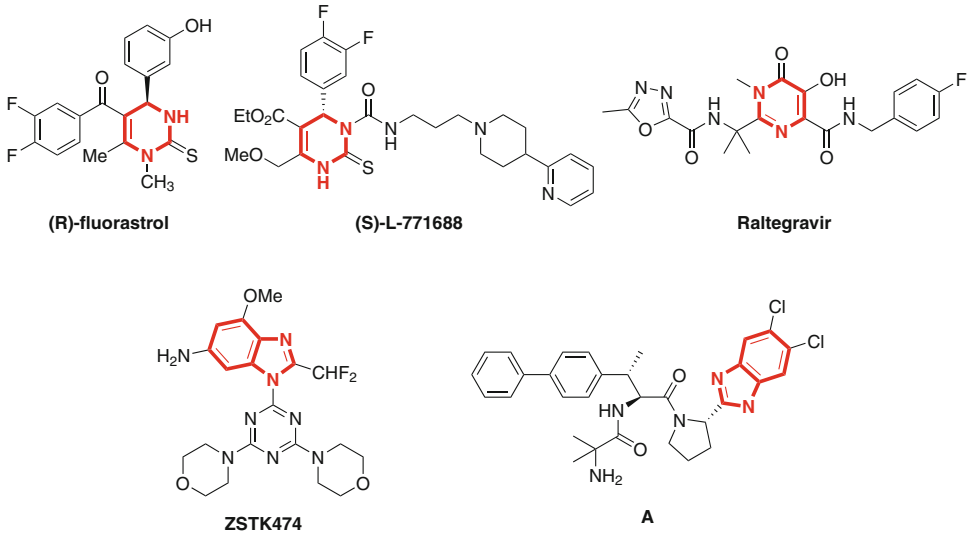


Fig. 1 Heterocycles containing dihydropyrimidines and benzimidazole frameworks

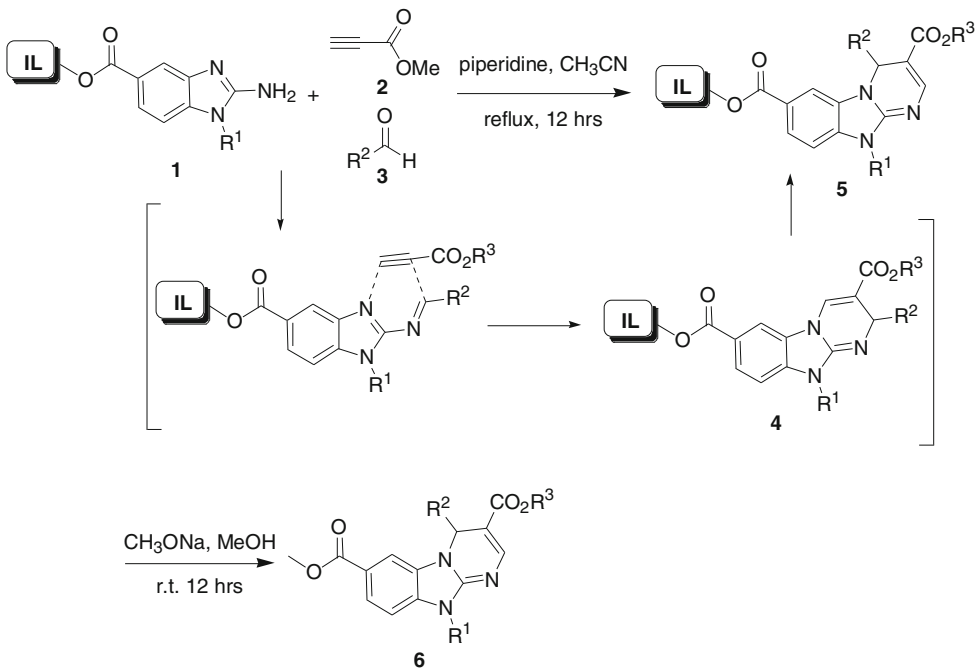
an effort to develop a practical approach toward the structural class of benzimidazole-fused dihydropyrimidines, we envisaged a possible Lewis base-catalyzed, one pot three-component condensation of electron-deficient dienophiles with IL-anchored 2-aminobenzimidazoles.

Ionic liquids (ILs) have received considerable attention in the recent research community as the highly customizable solvents for almost any synthetic purpose [14]. Recently, ILs have attracted widespread interest as novel green reaction media and reagents for various chemical tasks due to their unique physical properties [15,16]. Aside from the homogeneous reaction conditions and high loading capacity, ionic liquid supports have several other attractive advantages such as the reaction progress can be monitored by conventional NMR analysis. The excess amounts of reagents and byproducts are removed by simple washing with low-polar organic solvents [17]. Furthermore, the high polarity and ionic character of ionic-liquid support have proven to exert synergistic effects and reaction rate enhancements [18]. These advantageous IL features inspire that they are utilized as soluble supports in organic synthesis. In this report, we present a highly efficient ionic liquid supported synthesis of novel benzimidazole fused dihydropyrimidine derivatives catalyzed by Lewis base.

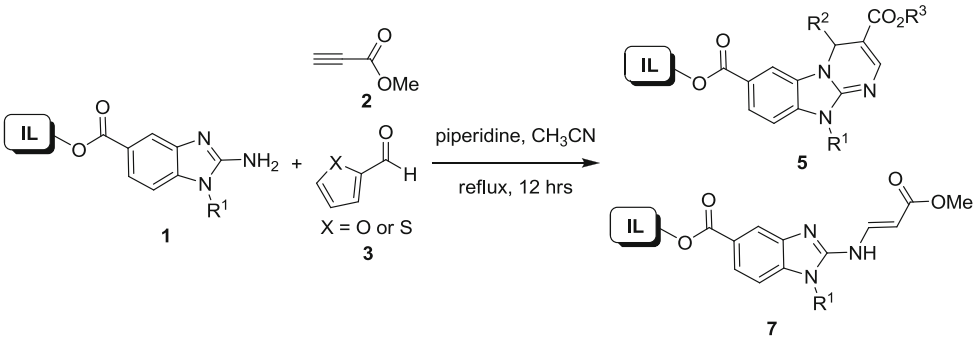
Results and discussion

3-Hydroxyethyl(1-methylimidazolium)tetrafluoroborate, as an ionic soluble support (IL), is readily available from the reaction of 1-methylimidazole and 2-bromoethanol for the exploration of current multicomponent reaction [19,20]. The IL immobilized 2-amino benzo[*d*]imidazole **1** was prepared through a four-step synthetic protocol to install the first diversity (R^1) in the growing skeleton [21]. A careful literature survey revealed that the multicomponent reaction involving aniline, aldehyde, and electron-rich olefins is usually catalyzed by Lewis or Brønsted acid, such as $BF_3(OEt)_2$ [22], phosphoric acid [11] and metal triflates [23–26]. However, application of Lewis or Brønsted bases as catalyst have not been explored to date. Furthermore, the presence of heavy transition metal impurities in the final products caused problem during purification [27]. The development of efficient and transition metal free processes will significantly improve the synthetic process toward the assembly of chimeric heterocycles. With the IL-immobilized 2-amino benzo[*d*]imidazole **1a** in hand, we studied the viability of the multicomponent reaction by a reaction of **1a** with methyl propiolate **2** and furfural **3**. IL-linked 2-aminobenzimidazole **1a** was treated with aldehyde, alkyne, and piperidine in acetonitrile under reflux for 12 h. By taking advantage of the distinct solubility feature of the IL-anchored substrate, the excess amounts of reagents and the reaction byproducts are easily removed by precipitation in ether which the IL conjugate substrate is insoluble. Accordingly, IL conjugates **4** were purified and obtained in good yields after washing with diethyl ether. The progress of the ionic liquid supported multicomponent reaction was directly monitored via ^{1}H NMR spectroscopy without cleaving the intermediates from the ionic liquid support. The final coupling product was obtained, whose structure was considered as **4** according to the predicted results (Scheme 1). With successful exploration of one pot reaction on the ionic liquid support, we tried to employ microwave irradiation on the same reaction to accelerate the reaction progress. Unfortunately, a complex mixture was obtained under MW. It is attributed to that the harsh reaction condition was created by the high-polar microwave absorbance medium, ionic-liquid support. Moreover, the reactivities of the aldehydes also play an important

Scheme 1 Piperidine-catalyzed one pot reaction and [1,5]sigmatropic rearrangement



Scheme 2 Observed by-products in multicomponent one-pot reaction



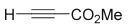
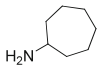
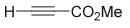
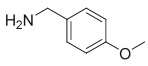
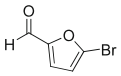
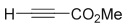
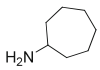
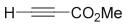
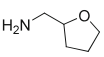
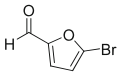
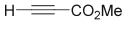
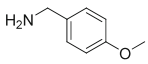
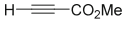
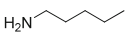
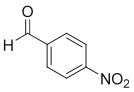
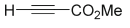
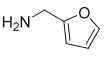
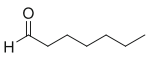
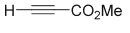
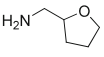
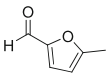
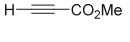
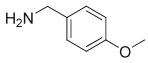
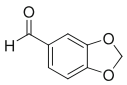
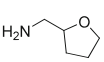
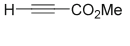
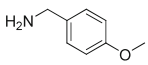
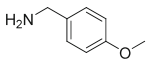
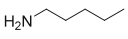
role in this multicomponent reaction. When inert aldehydes **3** were used, enamines **7** were isolated as the byproduct. In the case where furfural and thiophenecarboxaldehyde were applied, enamines **7** were the byproducts which diminished the yield of the condensed products **5** (Scheme 2).

The removal of the ionic liquid support from **5a** was carried out in sodium methoxide solution at ambient temperature in 12 hours to furnish 4,10-dihydropyrimido[1,2-*a*] benzimidazole derivative **6a**. The cleaved IL was precipitated from the reaction mixture by the addition of diethyl ether and the desired products were separated by filtration. The recovered IL was recycled for future use in the synthetic process. The filtrate was concentrated and the crude final compounds were subjected to HPLC analysis. This ionic liquid supported multicomponent reaction afforded crude benzimidazole embedded dihydropyrimidines with high HPLC purity (67–99 %). Further column chromatography furnished 4,10-dihydro- pyrimido-[1,2-*a*]benzimidazole **6** in good to excellent yield (Table 1, 70–98 %).

In addition to the spectroscopic studies, X-ray crystallography was carried out to confirm the structure and regioselectivity of the final products. To our surprise, the X-ray crystallographic revealed that the product structure is **5** instead of expected product **4**. The ORTEP diagram of compound **6a** is depicted in Fig. 2. The furanyl group is linked to the C2 carbon rather than the expected C11 carbon atom. This result clearly indicates the rearrangement of the initial reaction product **4** to dihydropyrimidobenzimidazole **5**. The furanyl group migrated from the C2 carbon to the C11 carbon through electronic rearrangement in the dihydropyrimidine ring system.

The putative mechanism for the piperidine-catalyzed imination of IL-conjugated 2-aminobenzoimidazoles **1** with aldehyde **3** is proposed in Scheme 3. Initially, piperidine reacted with aldehyde to form piperidinium hydroxide salt, which spontaneously reacted with 2-aminobenzoimidazoles **1** on the ionic liquid support to afford adduct **A** through the elimination of one equivalent of water. Finally, loss

Table 1 Reaction substrate scope of one pot reaction

Entry	R^1NH_2	R^2CHO	$H-\equiv-R^3$	HPLC purity (%)	isolate yield (%)[a]
6a				72	70
6b				74	72
6c				67	70
6d				70	70
6e				78	75
6f				89	85
6g				99	98
6h				94	93
6i				75	78
6j				88	85
6k				73	77
6l				93	92
6m				97	94
6n				97	92
6o				96	94
6p				70	75
6q				95	90
6r				84	85
6s				69	74
6t				95	90

[a] Yields were determined on weight of purified samples.

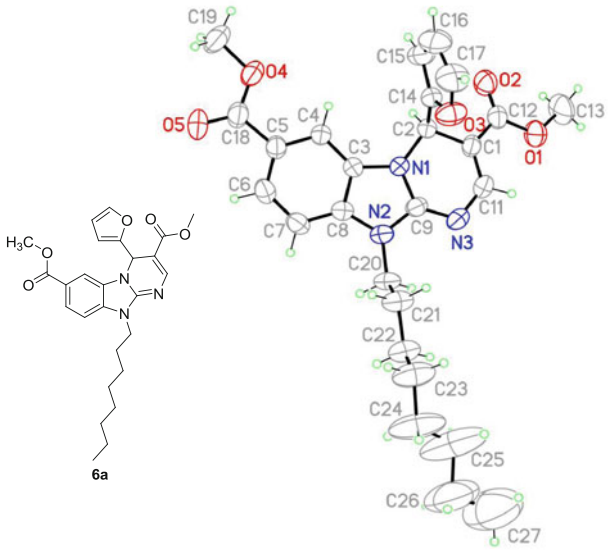


Fig. 2 ORTEP diagram of benzimidazolyl[1,2-*a*]dihydropyrimidine **6a**

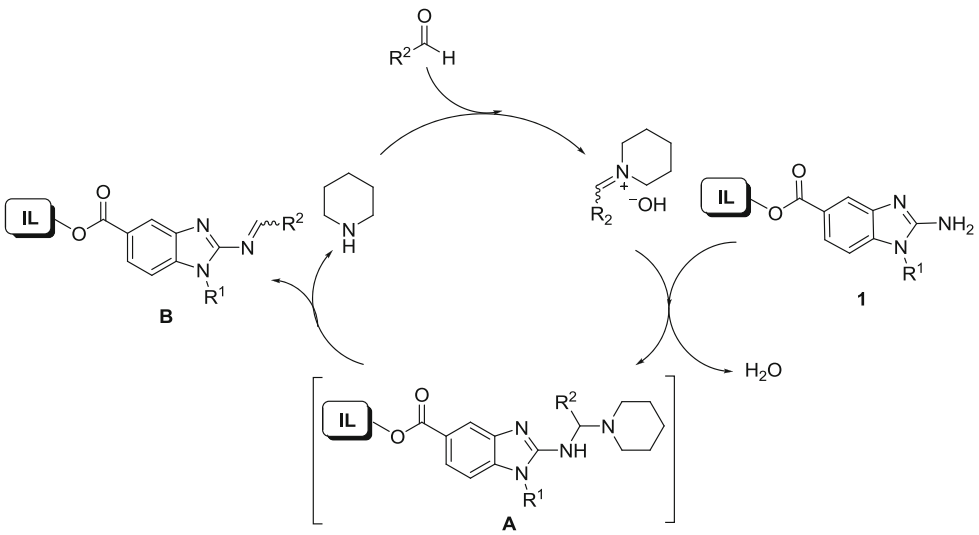
of piperidine from adduct **A** furnished imine product **B** [28]. Subsequently, the piperidine catalyzed cycloaddition between IL-tagged diazabutadienes **B** and electron deficient dienophile can proceed through a stepwise Mannich reaction followed by an intramolecular electrophilic aromatic substitution. The mechanism of the further rearrangement of **4** was envisioned through a series of electronic evolvement toward the formation of more stable conjugate system **5**. Finally, the [1,5]sigmatropic transfer of aryl or alkyl group could be triggered by the electron transfer on the acrylate to form a fully conjugated stable system through stabilization of the ionic intermediate to furnish dihydropyrimido[1,2-*a*]benzimidazole **5**.

With the successful exploration of IL-supported multicomponent rearrangement reaction under basic conditions, the multicomponent reaction of IL-supported 2-aminobenzimidazoles **1** with various aldehydes smoothly afforded the corresponding benzimidazolyl[1,2-*a*]dihydropyrimidine **6** with good yields after cleavage of the ionic liquid support. Enamine **7** was the byproduct which reduces the yield of the condensed compounds **6**. The substituents (R^1) on the IL bound 2-amino benzo[*d*]imidazole **1** show no significant effect on the yields of the multicomponent coupling reaction. This one-pot process worked well with a broad range of aldehydes to give the corresponding products in good yields. In sharp contrast to conventional multicomponent reaction which involves acid-catalyzed reaction of aniline, aromatic aldehydes electron-rich dienophiles, we have demonstrated the transition-metal-free, base-catalyzed multicomponent protocol can be applied to condensation of IL-bounded 2-amino benzo[*d*]imidazoles, electron-deficient acetylenes as well as aliphatic and heterocyclic aldehydes. In addition, ionic liquid supports allow for simple work-up procedures and straightforward protocols for products isolation through precipitation, particularly useful in multistep organic synthesis.

Conclusion

In summary, we have achieved the multicomponent condensation of 2-aminobenzimidazoles, aldehydes, and electron-deficient acetylenes to afford the benzimidazole fused dihydropyrimidines through novel sigmatropic rearrangement on the ionic liquid support. It is worth mentioning that ionic liquid-supported intermediates and the ionic liquid support itself are stable during the refluxing condition and their easy purification was performed through precipitation and washings. Particularly, monitoring reaction

Scheme 3 Proposed mechanism for piperidine-catalyzed imination



progress in each step by ^{1}H NMR is feasible with the ionic liquid support attached. This novel one-pot multicomponent reaction was utilized for the efficient synthesis of biologically promising novel chimeric scaffolds in high yields with excellent regioselectivity. The rapid synthesis and screening of focused combinatorial library including the union of these two privileged heterocycles will certainly provide ample opportunities to discover interesting biological activities.

General experimental methods

Methanol and acetone were distilled before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel coated plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (230–400 mesh). All the microwave experiments were performed in a Biotage initiator under optimized reaction conditions of power and pressure. ^{1}H NMR (300 mHz) and ^{13}C NMR (75 mHz) spectra were recorded on a 300 mHz spectrometer. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard.

General procedures for synthesis of benzimidazole-fused dihydropyrimidine (**6**)

Aldehyde **2** (1.32 mmol, 3.0 equiv.), alkyne (0.44 mmol, 1.0 equiv.) and piperidine (0.22 mmol, 0.5 equiv.) were added to a solution of ionic liquid supported aminobenzimidazole **1** (0.20 g, 0.44 mmol) in dry acetonitrile. The reaction mixture was refluxed for 12 h. After completion, the reaction mixture was precipitated and washed (50 mL × 3) with cold ether. The precipitate was filtered and dried to furnish the IL bound benzoimidazotriazine **5** in quantitative yield. CH_3ONa (0.01 g) was added to IL bound benzoimidazotriazine **5** (0.26 g, 0.44 mmol) in methanol (20 mL). The mixture was stirred at ambient temperature for 12 h. After completion of cleavage in the ionic support site, the inorganic salt was removed by filtration and then filtrate was concentrated under reduced pressure. The ionic liquid was precipitated out with excess of cold ether (50 mL × 3) and removed by filtration. The filtrate was dried and subjected to HPLC analysis which depicts high purity. The title compounds **5** were obtained in good to excellent overall yield after column chromatography purification.

*Dimethyl 4-(furan-2-yl)-10-octyl-4,10-dihydropyrimido [1,2-a] benzimidazole-3,7-dicarboxylate (**6a**)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 8.03–7.92 (m, 3H), 7.28 (d, J = 1.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.55 (s, 1H), 6.39 (d, J = 3.3 Hz, 1H), 6.26 (dd, J = 3.3, 1.8 Hz, 1H), 4.08 (m, 2H), 3.94 (s, 3H), 3.72 (s, 3H), 1.87–1.76 (m, 2H), 1.43–1.20 (m, 10H), 0.87 (t, J = 6.3 Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.0, 167.0, 153.1, 150.9, 149.3, 142.9, 134.9, 129.4, 125.7, 124.7, 111.4, 110.9, 108.9, 108.2, 100.2, 52.7, 51.6, 50.2, 42.8, 32.1, 29.6, 29.5, 28.7, 27.1, 23.0, 14.4; IR (cm^{-1}, neat): 2927, 1720, 1525; MS (EI-MS) m/z: 465 (M^+); HRMS: calcd for $C_{26}H_{31}N_3O_5$ m/z: 465.2264; Found 465.2253 (M^+).

*Mimethyl 10-cycloheptyl-4-(furan-3-yl)-4,10-dihydropyrimido[1,2-a] benzimidazole-3,7-dicarboxylate (**6b**)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.89 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.49 (s, 1H), 6.49 (s, 1H), 6.27 (s, 1H), 4.80 (s, 1H), 3.93 (s, 3H), 3.73 (s, 3H), 2.34–2.13 (m, 2H), 1.75–1.49 (m, 10H); ^{13}C NMR (75 mHz, $CDCl_3$)δ 167.1, 166.9, 150.7, 148.4, 143.9, 140.2, 133.8, 129.6, 125.6, 125.3, 124.3, 110.9, 110.2, 109.4, 102.3, 56.7, 52.7, 51.5, 48.7, 33.2, 33.0, 30.1, 27.8, 27.7, 26.0, 25.9; IR (cm^{-1}, neat): 2927, 1718, 1518; MS (EI-MS) m/z: 449 (M^+); HRMS: calcd for $C_{25}H_{27}N_3O_5$ m/z: 449.1951; Found 449.1945 (M^+).

*Dimethyl 4-(5-bromofuran-2-yl)-10-(4-methoxybenzyl)-4,10-dihydro- pyrimido[1,2-a]benzimidazole-3,7-dicarboxylate (**6c**)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.99 (d, J = 1.8 Hz, 1H), 7.99 (s, 1H), 7.89 (dd, J = 8.3, 1.2 Hz, 1H), 7.31–7.25 (m, 2H), 7.06 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 6.85 (s, 1H), 6.54 (s, 1H), 6.42 (d, J = 3.3 Hz, 1H), 6.21 (d, J = 3.3 Hz, 1H), 5.29 (s, 2H), 3.94 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.9, 154.6, 151.2, 134.7, 129.3, 129.3, 129.2, 127.2, 126.0, 125.0, 122.5, 114.8, 112.8, 111.0, 111.3, 109.0, 99.8, 55.7, 52.7, 51.7, 50.4, 45.7; IR (cm^{-1}, neat): 2927, 1718, 1518; MS (EI-MS) m/z: 551 (M^+); HRMS: calcd for $C_{26}H_{22}BrN_3O_6$ m/z: 551.0692; Found 551.0693 (M^+).

*Dimethyl 10-cycloheptyl-4-(furan-2-yl)-4,10-dihydropyrimido[1,2-a] benzimidazole-3,7-dicarboxylate (**6d**)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.99 (s, 1H), 7.96 (s, 1H), 7.89 (dd, J = 8.4, 1.5 Hz, 1H), 7.28 (d, J = 1.5 Hz, 2H), 6.54 (s, 1H), 6.38 (d, J = 3.3 Hz, 1H), 6.26 (dd, J = 3.3, 1.8 Hz, 1H), 4.81 (m, 1H), 3.94 (s, 3H), 3.72 (s, 3H), 2.29–2.14 (m, 2H), 2.10–1.57 (m, 10H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.1, 167.0, 153.2, 150.3, 149.4, 142.9, 133.6, 129.8, 125.3, 124.3, 111.3, 110.9, 110.2, 108.9, 99.8, 56.7, 52.7, 51.6, 50.2, 33.1, 33.0, 27.8, 27.7, 26.0, 25.9; IR (cm^{-1}, neat): 2927, 1720, 1519; MS (EI-MS) m/z: 449 (M^+); HRMS: calcd for $C_{25}H_{27}N_3O_5$ m/z: 449.1951; Found 449.1948 (M^+).

*Dimethyl 4-(5-bromofuran-2-yl)-10-(tetrahydrofuran-2-ylm-ethyl)- 4,10-dihydropyrimido[1,2-a]benzimidazole-3,7-dicarboxylate (***6e***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.99–7.92 (m, 3H), 7.38 (d, J = 8.4 Hz, 1H), 6.52 (s, 1H), 6.41 (d, J = 3.3 Hz, 1H), 6.20 (d, J = 3.3 Hz, 1H), 4.33 (m, 1H), 4.28 (dd, J = 14.4, 3.3 Hz, 1H), 4.16 (dd, J = 14.4, 6.0 Hz, 1H), 3.96 (s, 3H), 3,74 (s, 3H), 3.70 (m, 1H), 2.10 (m, 1H), 1.82–1.70 (m, 4H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.0, 166.9, 154.6, 151.3, 149.5, 135.7, 129.0, 125.9, 124.9, 122.3, 112.8, 111.5, 111.0, 110.1, 99.6, 68.8, 52.7, 51.7, 50.3, 50.3, 46.8, 29.0, 26.2; IR (cm^{-1}, neat): 2927, 1716, 1525; MS (EI-MS) m/z: 515 (M^+); HRMS: calcd for $C_{23}H_{22}BrN_3O_6$ m/z: 515.0692; Found 515.0690 (M^+).

*Dimethyl 4-cyclohexyl-10-(4-methoxybenzyl)-4,10-dihydropyrimido [1,2-a]benzimidazole-3,7-dicarboxylate (***6f***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.94 (s, 1H), 7.91–7.83 (m, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.85 (dd, J = 6.9, 1.8 Hz, 2H), 5.54 (d, J = 2.7 Hz, 1H), 5.33 and 5.25 (Abq, J = 15.7 Hz, 2H), 3.95 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 1.97–1.40 (m, 11H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 168.0, 167.1, 159.8, 153.0, 150.5, 134.8, 130.0, 129.2, 127.5, 125.3, 124.6, 114.7, 111.2, 108.8, 101.0, 57.0, 55.7, 52.7, 51.6, 46.1, 45.5, 30.0, 27.9, 26.6, 26.6, 26.4; IR (cm^{-1}, neat): 2927, 1718, 1516; MS (EI-MS) m/z: 489 (M^+); HRMS: calcd for $C_{28}H_{31}N_3O_5$ m/z: 489.2264; Found 489.2276 (M^+).

*Dimethyl 4-(4-nitrophenyl)-10-pentyl-4,10-dihydropyrimido[1,2-a] benzimidazole-3,7-dicarboxylate (***6g***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 8,15 (d, J = 8.7 Hz, 2H), 7.89 (s, 1H), 7.92 (dd, J = 8.4, 1.2 Hz, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.55 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 4.15 (t, J = 7.5 Hz, 2H), 3.88 (s, 3H), 3.67 (s, 3H), 1.89–1.79 (m, 2H), 1.43–1.32 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 166.8, 166.6, 151.2, 148.6, 148.1, 148.0, 134.9, 128.9, 128.5, 126.1, 125.0, 124.5, 110.9, 108.6, 102.9, 57.0, 52.8, 51.6, 42.9, 29.2, 28.4, 22.7, 14.4; IR (cm^{-1}, neat): 2952, 1720, 1525; MS (EI-MS) m/z: 478 (M^+); HRMS: calcd for $C_{25}H_{26}N_4O_6$ m/z: 478.1852; Found 478.1862 (M^+).

*Dimethyl 10-(furan-2-ylmethyl)-4-hexyl-4,10-dihydropyrimido[1,2-a] benzimidazole-3,7-dicarboxylate (***16h***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.95 (dd, J = 8.4, 1.2 Hz, 1H), 7.87 (s, 2H), 7.36 (d, J = 1.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 6.41 (d, J = 3.3 Hz, 1H), 6.34 (dd, J = 3.3, 1.8 Hz, 1H), 5.70 (t, J = 4.2 Hz, 1H), 5.29 and 5.23 (Abq, J = 15.7 Hz, 2H), 3.96 (s, 3H), 3.79 (s, 3H), 1.99 (m, 1H), 1.85–1.72 (m, 3H), 1.49–1.27 (m, 2H), 1.20–1.17 (m, 2H), 0.94–0.81 (m, 2H), 0.79 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.4, 167.0, 152.3, 149.9, 148.6, 143.3, 134.7, 129.4, 125.6, 125.0, 111.1, 110.5, 109.7, 109.0, 101.8, 53.3, 52.7, 51.6, 39.0, 33.1, 32.0, 29.4, 23.1, 22.8, 14.4; IR (cm^{-1}, neat): 2927, 1720, 1520; MS (EI-MS) m/z: 451 (M^+); HRMS: calcd for $C_{25}H_{29}N_3O_5$ m/z: 451.2107; Found 451.2104 (M^+).

*Dimethyl 4-(5-methylfuran-2-yl)-10-(tetrahydrofuran-2-ylmethyl)- 4,10-dihydropyrimido[1,2-a]benzimidazole-3,7-dicarboxylate (***6i***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 8.08–7.91 (m, 3H), 7.35 (d, J = 8.4 Hz, 1H), 6.48 (s, 1H), 6.26 (dd, J = 5.3, 3.2 Hz, 1H), 5.85 (d, J = 3.3 Hz, 1H), 4.37–4.26 (m, 2H), 4.12 (m, 1H), 3.95 (s, 3H), 3.89–3.63 (m, 3H), 3.73 (s, 3H), 3.50 (t, J = 5.7 Hz, 1H), 3.32 (t, J = 5.7 Hz, 1H), 2.18 (d, J = 6.3 Hz, 3H), 2.12 (m, 1H), 1.93–1.50 (8H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.1, 152.7, 151.2, 149.2, 149.0, 135.8, 131.3, 129.2, 125.7, 124.7, 111.5, 109.9, 109.6, 107.0, 100.5, 68.7, 52.6, 51.6, 50.4, 46.8, 29.3, 26.1, 14.1; IR (cm^{-1}, neat): 2927, 1718, 1525; MS (EI-MS) m/z: 451 (M^+); HRMS: calcd for $C_{24}H_{25}N_3O_6$ m/z: 451.1743; Found 451.1733 (M^+).

*Dimethyl 4-(1,3-benzodioxol-5-yl)-10-(4-methoxybenzyl)-4,10- dihydropyrimido[1,2-a]benzimidazole-3,7-dicarboxylate (***6j***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.91 (s, 1H), 7.81 (dd, J = 8.4, 1.5 Hz, 1H), 7.67 (d, J = 1.5 Hz, 1H), 7.28 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.85–6.90 (m, 3H), 6.73 (d, J = 7.8 Hz, 1H), 6.37 (s, 1H), 5.90 (dd, J = 7.2, 1.5 Hz, 2H), 5.30 and 5.22 (ABq, J = 15.6 Hz, 2H), 3.89 (s., 3H), 3.79 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.1, 166.9, 159.9, 151.5, 148.6, 148.0, 147.8, 135.4, 134.8, 129.5, 129.3, 127.4, 125.7, 124.8, 121.4, 114.8, 111.4, 108.8, 108.4, 107.9, 104.4, 101.6, 57.5, 55.7, 52.7, 51.5, 45.6; IR (cm^{-1}, neat): 2927, 1720, 1520; MS (EI-MS) m/z: 527 (M^+); HRMS: calcd for $C_{29}H_{25}N_3O_7$ m/z: 527.1693; Found 527.1697 (M^+).

*Dimethyl 4-(furan-2-yl)-10-(tetrahydrofuran-2-ylmethyl)-4,10- dihydropyrimido[1,2-a]benzimidazole-3,7-dicarboxylate (***6k***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.99 (d, J = 1.2 Hz, 1H), 7.97–7.92 (m, 2H), 7.35 (dd, J = 8.4, 3.0 Hz, 1H), 7.28 (m. 1H), 6.56 (s, 1H), 6.40 (t, J = 3.0 Hz, 1H), 6.27 (dd, J = 3.0, 1.8 Hz, 1H), 4.40–4.25 (m, 2H), 4.10 (m, 1H), 3.94 (s, 3H), 3.88–3.65 (m, 2H), 3.73 (s, 3H), 2.10 (m, 1H), 1.94–1.72 (m, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.1, 167.0, 153.0, 153.0. 151.3, 151.3, 149.3, 149.2, 142.9, 135.7, 135.6, 129.3, 129.2, 125.8, 124.8, 124.8, 111.2, 111.1, 109.9, 109.8, 109.0, 108.9, 100.4, 68.7, 52.7, 51.6, 50.2, 46.8, 29.3, 29.1, 26.1; IR (cm^{-1}, neat): 2950, 1724, 1523; MS (EI-MS) m/z: 437 (M^+); HRMS: calcd for $C_{23}H_{23}N_3O_6$ m/z: 437.1587; Found 437.1590 (M^+).

*Dimethyl 10-(4-methoxybenzyl)-4-(propan-2-yl)-4,10-dihydro -pyrimido[1,2-a]benzimidazole-3,7-dicarboxylate (***6l***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 (s, 1H), 7.86 (dd, J = 8.4, 1.4 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 5.61 (d, J = 2.7 Hz, 1H), 5.28 and 5.15 (ABq, J = 15.3 Hz, 2H), 3.94 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.26 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$)δ 168.0, 167.6, 159.8, 153.0, 150.8, 134.8, 129.9, 129.2, 127.5, 125.4, 124.6, 114.7, 111.2, 108.8, 100.5, 57.4 55.7, 52.7, 51.6, 45.5, 35.6, 19.5, 17.6; IR (cm^{-1}, neat): 2950, 1718, 1525; MS (EI-MS) m/z: 449 (M^+); HRMS: calcd for $C_{25}H_{27}N_3O_5$ m/z: 449.1951; Found 449.1938 (M^+).

*Dimethyl 10-(4-methoxybenzyl)-4-propyl-4,10-dihydropyrimido [1,2-a]benzimidazole-3,7-dicarboxylate (***6m***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.88 (s, 2H), 7.86 (dd, J = 3.0, 1.5 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.72 (dd, J = 4.2, 3.0 Hz, 1H), 5.21 and 5.18 (ABq, J = 15.3 Hz, 2H), 3.94 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 2.10–1.90 (m, 2H), 1.77 (m, 1H), 1.48 (m, 1H), 0.80 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.5, 167.0, 159.8, 152.7, 150.2, 134.8, 129.4, 129.2, 127.5, 125.5, 124.8, 114.7, 110.5, 108.9, 101.6, 55.7, 53.3, 52.7, 51.5, 45.5, 35.4, 16.7, 14.3; IR (cm^{-1}, neat): 2952, 1716, 1529; MS (EI-MS) m/z: 449 (M^+); HRMS: calcd for $C_{25}H_{27}N_3O_5$ m/z: 449.1951; Found 449.1938 (M^+).

*Dimethyl 10-pentyl-4-(propan-2-yl)-4,10-dihydropyrimido [1,2-a] benzimidazole-3,7-dicarboxylate (***6n***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.96 (dd, J = 8.4, 1.2 Hz, 1H), 7.92 (s, 2H), 7.15 (d, J = 8.4 Hz, 1H), 5.59 (d, J = 2.7 Hz, 1H), 4.19–3.95 (m, 3H), 3.97 (s, 3H), 3.78 (s, 3H), 2,20 (m, 1H), 1.85–1.73 (m, 2H), 1.30–1.25 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 168.1, 167.1, 152.7, 150.8, 135.1, 129.8, 125.3, 124.4, 111.2, 108.2, 100.2, 57.3, 52.7, 51.5, 42.6, 35.7, 29.2, 28.4, 22.7, 19.5, 17.6, 14.3; IR (cm^{-1}, neat): 2956, 1718, 1522; MS (ESI-MS) m/z: 400 $(M+H)^+$; HRMS: calcd for $C_{22}H_{29}N_3O_4$ m/z: 399.2158; Found 399.2154(M^+).

*Dimethyl 4-ethyl-10-(4-methoxybenzyl)-4,10-dihydropyrimido[1,2-a] benzimidazole-3,7-dicarboxylate (***16o***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.91 (s, 1H), 7.87 (dd, J = 6.3, 1.5 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 6.3 Hz, 1H), 6.85 (dd, J = 6.3, 1.5 Hz, 2H), 5.75 (dd, J = 4.1, 2.4 Hz, 1H), 5.24 and 5.15 (ABq, J = 15.6 Hz, 2H), 3.93 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.11 (m, 1H), 1.83 (m, 1H), 0.76 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.5, 167.0, 159.8, 152.8, 150.4, 134.8, 129.4, 129.2, 127.5, 125.5, 124.8, 114.7, 110.6, 108.9, 100.8, 55.7, 53.9, 52.7, 51.5, 45.5, 25.7, 7.4; IR (cm^{-1}, neat): 2951, 1716, 1522; MS (EI-MS) m/z: 435 (M^+); HRMS: calcd for $C_{24}H_{25}N_3O_5$ m/z: 435.1794; Found 435.1787 (M^+).

*Dimethyl 4-benzyl-10-(furan-2-ylmethyl)-4,10-dihydropyrimido [1,2-a]benzimidazole-3,7-dicarboxylate (***6p***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.97 (dd, J = 8.4, 1.5 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.68 (s, 1H), 7.40–7.35 (m, 2H), 7.26 (m, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 7.5 Hz, 2H), 6.64 (dd, J = 6.9, 1.2 Hz, 2H), 6.34 (dd, J = 3.3, 1.8 Hz, 2H), 5.13 and 4.96 (ABq, J = 15.9 Hz, 2H), 3.97 (s, 3H), 3.84 (s, 3H), 3.29 (dd, J = 14.1, 3.6 Hz, 1H), 2.97 (dd, J = 14.1, 3.6 Hz, 1H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.4, 167.0, 151.8, 150.3, 148.5, 143.2, 136.2, 134.5, 130.0, 129.4, 128.3, 127.2, 125.7, 125.0, 111.1, 110.8, 109.8, 109.0, 101.0, 54.5, 52.7, 51.7, 38.8, 38.7; IR (cm^{-1}, neat): 2927, 1716, 1525; MS (ESI-MS) m/z: 458 $(M+H)^+$; HRMS: calcd for $C_{26}H_{23}N_3O_5$ m/z: 457.1638; Found 457.1637 (M^+).

*Dimethyl 10-(furan-2-ylmethyl)-4-(2-phenylethyl)-4,10-dihydropyrimido[1,2-a]benzimidazole-3,7-dicarboxylate (***6q***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.95 (s, 1H), 7.91 (dd, J = 8.4, 1.5 Hz, 1H), 7.83 (d, J = 1.0 Hz, 1H), 7.36 (m, 1H), 7.16

(d, $J = 8.4$ Hz, 1H), 7.17–7.10 (m, 3H), 6.97–6.91 (m, 2H), 6.40 (d, $J = 3.3$ Hz, 1H), 6.33 (dd, $J = 3.3$, 1.8 Hz, 1H), 5.80 (t, $J = 3.3$ Hz, 1H), 5.20 and 5.03 (Abq, $J = 15.9$ Hz, 2H), 3.95 (s, 3H), 3.81 (s, 3H), 2.81 (m, 1H), 2.57–2.31 (m, 2H), 2.20 (m, 1H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.4, 167.0, 152.0, 150.4, 148.5, 143.4, 141.1, 134.6, 129.2, 128.4, 128.3, 126.0, 125.6, 124.9, 111.1, 110.5, 109.8, 108.9, 100.9, 53.2, 52.7, 51.6, 38.9, 33.2, 29.5; IR (cm^{-1}, neat): 2949, 1716, 1529; MS (EI-MS) m/z: 471 (M^+); HRMS: calcd for $C_{27}H_{25}N_3O_5$ m/z: 471.1794; Found 471.1786 (M^+).

*Dimethyl 10-(furan-2-ylmethyl)-4-(5-methylfuran-2-yl)-4,10- dihydropyrimido[1,2-a]benzimidazole-3,7-dicarboxylate (***6r***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 8.04 (d, $J = 1.5$ Hz, 1H), 7.97 (s, 1H), 7.92 (dd, $J = 8.4$, 1.5 Hz, 1H), 7.36 (dd, $J = 1.8$, 0.7 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 6.48 (s, 1H), 6.42 (d, $J = 3.2$ Hz, 1H), 6.34 (dd, $J = 3.2$, 1.8 Hz, 1H), 6.26 (d, $J = 3.2$ Hz, 1H), 5.85 (dd, $J = 3.2$, 0.9 Hz, 1H), 5.31 and 5.23 (ABq, $J = 15.9$ Hz, 2H), 3.94 (s, 3H), 3.73 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.1, 167.0, 152.7, 151.2, 150.7, 149.0, 148.5, 143.4, 134.6, 129.5, 125.8, 125.0, 111.6, 111.1, 109.9, 109.9, 108.8, 107.0, 100.7, 52.7, 51.6, 50.5, 39.0, 14.0; IR (cm^{-1}, neat): 2951, 1718, 1525; MS (EI-MS) m/z: 471 (M^+); HRMS: calcd for $C_{24}H_{21}N_3O_6$ m/z: 471.1794; Found 471.1786 (M^+).

*Dimethyl 4-(5-bromofuran-2-yl)-10-pentyl-4,10-dihydropyrimido [1,2-a]benzimidazole-3,7-dicarboxylate (***6s***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 8.00 (s, 1H), 7.97 (d, $J = 1.2$ Hz, 1H), 7.96 (s, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 6.52 (s, 1H), 6.39 (d, $J = 3.3$ Hz, 1H), 6.20 (d, $J = 3.3$ Hz, 1H), 4.10 (t, $J = 6.9$ Hz, 2H), 3.96 (s, 3H), 3.74 (s, 3H), 1.87–1.78 (m, 2H), 1.41–1.31 (m, 4H), 0.91 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 166.9, 166.9, 154.7, 150.8, 149.6, 134.9, 129.2, 125.9, 124.8, 122.4, 112.8, 111.6, 111.4, 108.4, 99.3, 52.7, 51.7, 50.3, 42.8, 29.2, 28.4, 22.7, 14.3; IR (cm^{-1}, neat): 2929, 1720, 1525; MS (EI-MS) m/z: 501 (M^+); HRMS: calcd for $C_{23}H_{24}BrN_3O_5$ m/z: 501.0899; Found 501.0898 (M^+).

*Dimethyl 4-ethyl-10-(furan-2-ylmethyl)-4,10-dihydropyrimido [1,2-a]benzimidazole-3,7-dicarboxylate (***6t***)*

^{1}H NMR (300 mHz, $CDCl_3$) δ 7.94 (dd, $J = 8.4$, 1.5 Hz, 1H), 7.90 (s, 1H), 7.85 (d, $J = 1.5$ Hz, 1H), 7.36 (dd, $J = 1.8$, 0.6 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 6.39 (dd, $J = 3.3$, 3.0 Hz, 1H), 6.33 (dd, $J = 3.3$, 1.8 Hz, 1H), 5.72 (dd, $J = 3.9$, 2.7 Hz, 1H), 5.27 and 5.21 (ABq, $J = 15.9$ Hz, 2H), 3.95 (s, 3H), 3.78 (s, 3H), 2.11 (m, 1H), 1.84 (m, 1H), 0.74 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 mHz, $CDCl_3$) δ 167.4, 167.0, 152.4, 150.3, 148.6, 143.4, 134.8, 129.3 125.6, 124.9, 111.1, 110.5, 109.7, 108.9, 101.1, 53.9, 52.7, 51.6, 39.0, 25.8, 7.4; IR (cm^{-1}, neat): 2929, 1720, 1525; MS (EI-MS) m/z: 395 (M^+); HRMS: calcd for $C_{21}H_{21}N_3O_5$ m/z: 395.1481; Found 395.1492 (M^+).

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